REMARKS

I. Pending Claims

Claims 23, 29, 73, and 76-77 are pending as listed. Applicant respectfully notes that, contrary to the Examiner's description, the currently pending claims are not exactly in the same condition as they were in the claim set filed 06/17/2009, since the pending claim 77 was not present in June 17, 2009 amendment. Office Action at page 2. Applicant respectfully submits that the pending claims are allowable for the following reasons.

II. Arguments and Response to Rejection

1. Claim Rejections Under 35 U.S.C. § 103

The Examiner has reinstated the rejection of Claims 23, 29, 73 and 76-77 under 35 U.S.C. § 103(a) as obvious over Vogelsang *et al.* (*N. Engl. J. Med.*, 1992, vol. 326, pages 1055-1058, "Vogelsang") in view of Kaplan (U.S. Patent No. 5,385,901, "Kaplan"). Office Action at pages 3-4. The Examiner alleges that Vogelsang discloses the administration of thalidomide to patients with chronic graft-versus-host disease ("GVHD") whose primary diagnosis was chronic myelogenous leukemia (Table 1), and thus the reference teaches the administration of thalidomide to patients having blood-born tumors and leukemia. *Id.* Applicant respectfully disagrees. Applicant reiterates that the instant claims are not *prima facie* obvious over Vogelsang in view of Kaplan for the reasons set forth in all of Applicant's Responses of record, which are explained below.

A. *Vogelsang does not render the claimed invention obvious*

Applicant further maintains that the present invention is indeed nonobvious over the Vogelsang reference and that the rejection based on it should be withdrawn because the Vogelsang article is analogous to the disclosure at issue in *Chen v. Bouchard*, 347 F.3d 1299, 68 USPQ2d 1705 (Fed. Cir. 2003), which the court found was not adequate to establish inherent obviousness (which is the Examiner's contention here), specifically because it lacked any analytical data and other characteristics showing possession directly related to the claimed technology. *See* Exhibit 1 (copy of *Chen v. Bouchard*).

The Vogelsang authors state that they only "present a preliminary report of the use of thalidomide to treat patients with high-risk chronic GVHD and patients with refractory GVHD," not blood-born tumors or leukemia, and only present analytical data directed

narrowly to GVHD treatment. Vogelsang at page 1055. Thus, in the instant case, the Vogelsang reference does not disclose any analytical data or characteristic evidence directly related to treating angiogenic dependent or angiogenic associated diseases or disorders (*e.g.* blood-born tumors or leukemia), because the data presented are limited only to infections and GVHD.

Thus, as in *Chen*, there is no support here for the Examiner's determination that Vogelsang is inherently obvious because it does not disclose any analytical data or characteristic evidence of a treatment for angiogenic dependent or angiogenic associated blood-born tumors or leukemia showing that the authors were in possession of Applicant's claimed invention, merely that they were allegedly in possession only of a treatment of GVHD. In fact, Vogelsang itself does not purport even to demonstrate the relative efficacy of treating GVHD, noting instead that "[a] trial comparing thalidomide with prednisone in patients with newly diagnosed chronic GVHD will be required." (*emphasis added*) Vogelsang at Abstract. Thus, as in *Chen*, where the reference at issue was not adequate to establish a case of obviousness because it did not disclose any analytical data or other characteristic evidence directed specifically toward the claimed invention, it would be reasonable in the instant case for a person of ordinary skill in the art to conclude that any reported therapeutic effect in Vogelsang was consistent only with the amelioration of GVHD specifically, not tumors or leukemia. Indeed, the Vogelsang study likewise does not disclose any analytical data or other characteristic evidence directed specifically toward treating tumors or leukemia as claimed.

In addition, the Applicant respectfully contends that a person of ordinary skill in the art would not have had a reasonable expectation of success in using thalidomide to treat blood-born tumors or especially to treat leukemia in view of the disclosure in Vogelsang. The Examiner points to Table 1 in Vogelsang for the contention that some of the patients enrolled in the GVHD study had a primary diagnosis of chronic myelogenous leukemia and that consequently the reference inherently teaches treatment of leukemia with thalidomide. Office Action at page 3. However, the Vogelsang authors note with particularity that one of the patients enrolled in their study died because of a relapse of leukemia following treatment with thalidomide. Vogelsang at page 1057. Accordingly, even if there is arguably a suggestion in the art for a certain treatment, if one of ordinary skill would not have a reasonable expectation of therapeutic success for the treatment, then the claimed treatment may not be deemed obvious. *See Noelle v. Lederman*, 355 F.3d 1343, 1352-53 (Fed. Cir. 2004) (affirming a determination of non obviousness by the Board of Patent Appeals and

Interferences where it was undisputed that there was a motivation in the art to obtain certain isolated antibodies, but there was no reasonable expectation of success in so doing); *see also Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1354 (Fed. Cir. 2003) (affirming trial court's denial of JMOL motion concerning jury's finding that claimed process for isolating a certain virus was not obvious where, although there was a suggestion to do so in the art, the art reported failures using similar processes). Similarly, merely because a claimed invention may be obvious to try in light of the art, absent a concomitant finding that the art would lead one skilled in the art to believe that there was a reasonable likelihood of success, then the claimed invention may not be deemed obvious. *See Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1207-08 (Fed. Cir. 1991) (affirming district court's finding of non obviousness where probing a screening method used to isolate claimed genes was obvious to try in light of the art, but there was no reasonable expectation of success). Applicant respectfully contends that a person of ordinary skill in the art would not have had a reasonable expectation of success in using thalidomide to treat blood-born tumors or especially to treat leukemia in view of the disclosure in Vogelsang that discourages and teaches away from said use by expressly noting that one of the patients in their study died because of a relapse of leukemia after treatment with thalidomide.

Indeed, the PTO has acknowledged that several references disclosed that thalidomide was ineffective in treating tumors in humans. (*See* pages 8-10, Office Action dated March 16, 2009; "Thus, in three separate studies, thalidomide was ineffective in inhibiting tumor growth in mouse models of cancer. Given this information, the skilled artisan would not reasonably expect thalidomide to be effective in treating tumors in humans." (page 8, last paragraph); "Thus, it is clear that the treatment of tumors in humans with thalidomide is extremely unpredictable and in the majority of cases completely ineffective." (page 9, last paragraph); "Thus, a preponderance of evidence suggests that treating tumors with thalidomide, particularly in humans, is extremely unpredictable and in most cases ineffective. Further, it is evident that thalidomide may actually have the complete opposite effect than those instantly." (page 10, second paragraph)).

Moreover, the court in *Chen* also found that the prior disclosure at issue in that case was not an inherently obvious teaching because it was shown that the claimed results were "surprising." *Chen*, 68 USPQ2d at 1710. In the instant case, the Examiner has previously acknowledged that Applicant's claimed results are surprising in withdrawing a rejection of the claims under 35 U.S.C. § 103(a) over Olson *et al.*, *Clinical Pharmacology and Therapeutics*, 1965, vol. 6, no. 3, pages 292-297, "in light of Applicant's arguments, the

Declarations of Professor Morgan and Dr. Ohno, and Applicant's evidence of unexpected results previously submitted." Office Action issued October 20, 2010 at page 6. Accordingly, the acknowledgement that the Applicant's claimed results are surprising, and particularly in light of the teaching away of Vogelsang with regard specifically to the death of a patient due to leukemia following thalidomide treatment, is further evidence that Vogelsang did not disclose possession of a treatment for angiogenic dependent or angiogenic associated blood-born tumors or leukemia.

As in *Chen*, where the court found that the prior references "would *not* have been recognized by a person of ordinary skill in the art at the time they were [published] as 'describing' (in the sense of the statute)" the invention of the claims at issue, a person of ordinary skill in the art at the time of Vogelsang's disclosure would not have recognized it as describing the treatment of pathological states created due to unregulated angiogenesis, and especially blood-born tumors or leukemia. *Chen*, 68 USPQ2d at 1711 (emphasis in original). Finally, the *Chen* court determined that, "[b]ecause that finding is supported by substantial evidence," the prior disclosure was not adequate to support a contention of inherent obviousness. *Chen*, 68 USPQ2d at 1711. Likewise, in the instant case where the Examiner himself has acknowledged Applicant's substantial evidence overcoming a previous rejection of obviousness as noted above, Vogelsang is also not adequate to support a contention of inherent obviousness, and the rejection based on it should be withdrawn.

B. ***Kaplan does not cure the deficiency of Vogelsang***

The Examiner maintains that Kaplan teaches the oral administration of thalidomide in controlling abnormal concentrations of TNF-α and that it would thus have been obvious to administer thalidomide to chronic myelogenous leukemia patients having GVHD via administration routes taught in Kaplan. Office Action at page 4. Applicant respectfully traverses this rejection.

Kaplan does not remedy the deficiency of Vogelsang for the same reasons argued above and for the reasons set forth in all of Applicant's Responses of record. In particular, arguably the only teaching in Vogelsang of actually treating leukemia or blood-born tumors with thalidomide, either expressly or inherently, is a teaching away wherein the authors note that one of the patients in their study died because of a relapse of leukemia after being administered with thalidomide treatment.[1] Kaplan reports on the TNF-α inhibition activity of

[1] Applicant does not concede there is such a teaching of treatment of leukemia or blood-born tumors.

thalidomide and its use for controlling abnormal concentrations of TNF-α in different diseases, Cachexia, septic shock and HIV infection (Abstract and Column 3). Again, this is not what is currently claimed (treating blood-born tumors). Thus, Kaplan teaches away from the treatment of the recited tumors by focusing on the use of thalidomide for treating the different diseases.

In fact, Kaplan discloses that TNF-α is associated with the destruction of tumor cells as its name suggests (Column 2, lines 60-62). Therefore, when reading the teaching of Kaplan, a skilled artisan would have understood that thalidomide is not effective in treating tumors, because thalidomide inhibits TNF-α production. Accordingly, Kaplan teaches away from what is claimed, or at least there is no motivation to combine the teachings of Vogelsang and Kaplan to treat tumors.

Therefore, a skilled person would have no reason to use thalidomide as disclosed in Kaplan for treating patients disclosed in Vogelsang, because the combined teachings do not provide the legally required reasonable expectation of success. The mere fact that references can be combined or modified does not render the resultant combination obvious where the art also suggests that the combination would be undesirable. *See In re Mills*, 916 F.2d 680 (Fed. Cir. 1990); *see also Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1372 (Fed. Cir. 2000) (quoting *In re Beattie*, 974 F.2d 1309, 1311-12 (Fed. Cir. 1992)). When analyzing a combination of two references under § 103, the appropriate inquiry must consider what the combined teachings of the references would have suggested to those of ordinary skill in the art. *See Brown & Williamson Tobacco Corp. v. Phillip Morris, Inc.*, 229 F.3d 1120, 1124-25 (Fed. Cir. 2000). Importantly, a disclosure constitutes a teaching away if it is found to criticize, discredit, or otherwise discourage the invention claimed, as does the Vogelsang reference in the instant case. *See In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004).

Applicant respectfully submits that since Vogelsang expressly criticizes, discredits, and otherwise discourages the claimed invention by disclosing the death of a GVHD patient due to leukemia despite treatment with thalidomide, the combination of Kaplan with Vogelsang does not provide the legally required reasonable expectation of success, and in no way renders the claimed invention obvious. Accordingly, Applicant respectfully requests the withdrawal of the rejection under 35 U.S.C. § 103(a) based on Vogelsang in view of Kaplan.

In view of the above, Applicant respectfully submits that the present application is in condition for allowance. A favorable disposition to that effect is respectfully requested. Should the Examiner not agree that all claims are allowable, then a further personal or telephonic interview is respectfully requested to discuss any remaining issues and to

accelerate the allowance of the above-identified application. Please charge any required fees to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

Date: August 31, 2011

By: Yeah-Sil Moon (Reg. No. 52,042)
For: Anthony M. Insogna (Reg. No. 35,203)
JONES DAY
222 East 41st Street
New York, NY 10017
Tel. (212) 326-3778